REMARKS

I. Introduction

In response to the Office Action dated March 20, 2009, Re-examination and re-consideration of the application is requested in view of the following remarks.

II. Prior Art Rejections

On page (4) of the Office Action, claims 14-15, 19, and 25-27 were rejected under 35 U.S.C. §103(a) as being unpatentable over Chenard, EP 0900568 (Chenard) in view of Skradski, Epilepsia, 2000 (Skradski) in further view of Dursun et al., Canadian Journal of Psychiatry, 2000 (Dursun).

Applicants respectfully traverse these rejections. In the sections below, Applicants' attorney reviews the invention recited in the claims and the references cited by the Patent Office. Applicants' attorney then identifies how a combination of these references cannot be used to render the invention recited in the claims obvious.

1. THE CLAIMED INVENTION AND THE CITED REFERENCES

A. The Claimed Invention

The invention recited in claim 14 relates to a method of treating dyskinesia in a subject comprising administering to the subject a therapeutically effective amount of a compound of the formula (I) as defined in claim 14, wherein the dyskinesia is manifest as chorea or dystonia. In this context, those of skill in this art understand that dyskinesias are pathologies that are distinct from other movement disorders such as Parkinson's disease and/or myoclonus. Those of skill in the art further understand that dyskinesias are a common side effect of agents (such as L-Dopa) that are used to treat Parkinson's disease.

B. EP 0900568 to Chenard *et al.*

Chenard discloses a method of treating dyskinesia resulting from the use of dopamine agonist therapy by administering antagonists of the AMPA subtype of the glutamate receptor (see, e.g., paragraphs 1 to 4, 10, 13 and 15 of Chenard). As acknowledged by the Examiner at page 4 of the outstanding Office Action, although Chenard discloses a large number of compounds as being

suitable AMPA receptor antagonists (see paragraphs 5 and 6 of Chenard), Chenard nonetheless fails to teach or suggest the use of a compound of formula (I) of current claim 14 as an agent for treating dyskinesia, MUCH LESS for treating dyskinesia that is manifest as chorea or dystonia.

C. Skradski (*Epilesia,* 2000)

Skradski discloses a study that evaluated topiramate antagonism of glutamate receptors activated by kainate (see summary and first paragraph on page S45 of Skradski). Skradski suggests the possibility that topiramate has an effect on AMPA receptors from the effect of the compound DNQX, a compound which does not specifically bind the AMPA receptor and is instead a non-selective (mixed) AMPA/kainate receptor antagonist. In view of this non-specific receptor binding, **Skradski states that one cannot use their studies to reach definitive conclusions about the mechanisms of action of topiramate** (see page S45, summary, right column, lines 7 and 8 of Skradski).

D. Dursun et al. (*Epilesia,* 2000)

Dursun *et al.* discloses the use of clozapine to treat chronic paranoid schizophrenia and teaches that this treatment causes myoclonic jerks in the hands, arms and shoulders as a side effect. Dursun further teaches that the myoclonic jerks were then treated with topiramate.

2. APPLICANTS' RESPONSE TO THE REJECTIONS UNDER 35 U.S.C. 103(a)

At page 5 of the outstanding Office Action, the Patent Office predicates the rejection under 35 U.S.C. §103(a) on the belief that:

> [I]t would have been obvious to one of ordinary skill in the art at the time of the invention to have employed an AMPA receptor antagonist as a treatment for dyskinesia as taught by Chenard and also employed topiramate. **The motivation, provided by Skradski, teaches that topiramate possesses AMPA receptor antagonist properties. Thus one would expect with a reasonable degree of success that the treatment of dyskinesia with one AMPA receptor agonist over another would be equally successful, in the absence of unexpected results.** Additionally, one would be further encouraged that the employment of topiramate in the treatment of dyskinesia would be successful in light of the teachings of Dursun. As discussed above, Dursun teaches that topiramate is able to improve myoclonic jerks in the patient (which also arises as a side effect of a drug). As set forth on

record, Chenard teaches that **myoclonus is also encompassed by dyskinesia**. Thus as one of ordinary skill in the art would expect with a reasonable degree of success that topiramate would be able to treat the abnormal or uncontrollable movements associated with dyskinesia.

Applicants respectfully traverse this rejection because the skilled artisan would not agree with this technical analysis of the disclosures in Chenard, Skradski and Dursun.

To make the outstanding rejection, the Patent Office relies upon the Dursun reference's disclosure relating to myoclonus. However, as noted for example in Applicants' amendment submitted June 4, 2008, artisans in this field make a clear distinction between myoclonus and dyskinesia (e.g. dyskinesias that manifest as chorea or dystonia as recited in claim 14). Dyskinesias are clinically defined as: "abnormal, involuntary body movements that can appear as jerking, fidgeting, twisting, and turning movements". In contrast myoclonic jerks are a separate clinical phenomena, one characterized by sudden contractions of the big body muscles. Myoclonic jerks typically occur when a subject is falling asleep and cause a feeling of stumbling, falling or similar that subsequently cause a subject to wake up again. While almost everyone has experienced a myoclonic jerk while falling asleep, this experience does not result in a diagnosis of dyskinesia. This fundamental difference is borne out by the different responses to drug treatment. For example, myoclonus is treated with tranquilizers and anticonvulsants. In contrast, chorea and dystonia are not. Chorea can be abolished with dopamine receptor antagonists but there is no really effective medical treatment for dystonia. In view of the well established differences between dyskinesias (as recited in the claims) and myoclonus (as disclosed in Dursun), skilled artisan would not rely upon Dursun's disclosure of the use of topiramate to treat myoclonus as making topiramate's use in the treatment other movement disorders obvious (i.e. chorea or dystonia as recited in claim 14). Because the Chenard and Skradski disclosures fails to remedy these deficiencies in Dursun (much less motivate their combination), a combination of these references cannot render the claimed invention obvious.

As noted by the Patent Office at page 4, the Chenard patent application fails to provide any evidence that AMPA receptor antagonists having formula recited in claim 14 (e.g. topiramate) are useful in the treatment of dyskinesia. In addition, the Chenard patent application fails use the term "dyskinesia" according to its art-accepted definition. As noted above, dyskinesias are clinically

defined as: "abnormal, involuntary body movements that can appear as jerking, fidgeting, twisting, and turning movements" (see e.g. Applicants' amendment submitted June 4, 2008). In contrast to this definition, the drafter of the Chenard patent specification redefines this term so that it encompasses any abnormal or uncontrollable movement including, but not limited to, chorea, tremor, ballism, dystonia, athetosis, myoclonus and tic (see, e.g. paragraphs 2 and 13 of Chenard). As noted above, this characterization of myoclonus in the Chenard patent application conflicts with what is taught in this art. Consequently the skilled artisan could not rely on Chenard in the manner asserted by the Patent Office (i.e. as technical evidence that myoclonus is a pathological manifestation of dyskinesia). Moreover, the Chenard patent application further fails to provide any teaching or suggestion for the use AMPA receptor antagonists in the treatment of dyskinesia as defined in the current set of claims, i.e. dyskinesia that is manifest as chorea or dystonia. Because the Skradski and Dursun disclosures fails to remedy these deficiencies in the Chenard patent application (much less motivate their combination), a combination of these references cannot render the claimed invention obvious.

As noted for example in KSR v. Teleflex, 550 U.S. 398, 127 S. Ct. 1727 (2007), in determinations of obviousness under 35 U.S.C. §103(a), there must be some motivation to combine references. In this context, one of skill in the art would not agree with the Patent Office's belief that this motivation is provided by Skradski's disclosure that topiramate possesses AMPA receptor antagonist properties. Instead one of skill in this art would understand the significance of the portions of Skradski that teach that DNQX is a non-selective (mixed) AMPA/kainate receptor antagonist, and the associated text in Skradski that therefore warns artisans that their results "**preclude any definitive conclusions about the particular receptor subtype blocked by TPM [topiramate]" (**left column of page S47, lines 9-11). Skradski further teaches artisans that the effects of DNQX and topiramate are different and that, the topiramate blockade was dependent on the age of the cultures, i.e. it was effective in 11 day old cultures but was ineffective against 13 day or 14 day old cultures. Because of the ambiguities inherent in Skradski's studies (e.g. due to the high concentration of kainate used in the experiments) and their associated warning that this disclosure therefore precludes any definitive conclusions about the particular receptor subtype blocked topiramate, the skilled artisan would not rely on this disclosure to conclude that topiramate possesses AMPA receptor antagonist properties, much less make them expect with a reasonable

degree of success that the treatment of dyskinesia with one AMPA receptor agonist over another would be equally successful. For the reasons noted above, Skradski's teachings (e.g. that their results preclude definitive conclusions about the activity of topiramate) could not have motivated the skilled artisan to combine this disclosure with Chenard and Dursun in a manner that renders the claimed invention obvious.

In summary, because: (1) Dursun and Chenard fail to provide disclosures that teach information on dyskinesias that manifests as chorea or dystonia (i.e. as recited in claim 14); and further because (2) Skradski expressly warns artisans that their results preclude definitive conclusions about the activity of topiramate, a combination of these disclosures could not have motivated, much less led, the skilled person to arrive at the specific method recited in the current claims. For this reason, Applicants respectfully request a withdrawal of the rejections under 35 U.S.C. §103(a).

III. Conclusion

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Please consider this a PETITION FOR EXTENSION OF TIME for a sufficient number of months to enter these papers, if appropriate. Please charge all fees to Deposit Account No. 50-0494 of Gates & Cooper LLP.

Respectfully submitted,

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